SUNDAY – HMB-385

CB-012 - A Novel Antiviral-Fc Conjugate for Treatment and Prevention of Influenza Virus

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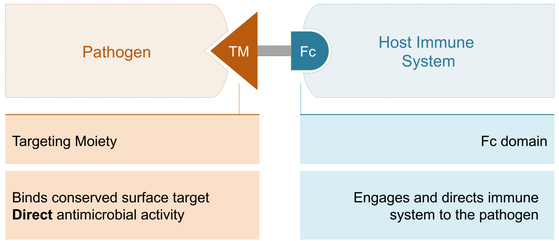
BACKGROUND

The World Health Organization has estimated up to 650,000 influenza-related respiratory deaths annually [1]. In the U.S., the 2017-2018 flu season was one of the most severe in recent history, having caused illness in ~50 million people and ~80,000 deaths [2].

While even healthy people are at risk of infection with seasonal flu, certain populations are particularly vulnerable and have higher risk of serious complications – young children, the elderly (people aged >65 years), pregnant women, people with chronic illness (e.g., diabetes, asthma, heart disease), and the immunocompromised [3]. Influenza vaccine effectiveness is only 40%, and current treatment approaches have limitations [4].

Cidara Therapeutics is using its Cloudbreak platform to develop a novel class of potent, long-acting antiviral Fc-conjugates (AVCs) against influenza that, in a single molecule, combine a surface-acting antiviral agent (targeting moiety; TM) with the Fc domain of a human IgG1 antibody (**Fig 1**). AVCs function by inhibiting viral replication while simultaneously engaging the immune system, providing a multimodal mechanism of action.

Figure 1. Cloudbreak platform of anti-infective conjugates



CB-012 is an AVC candidate being evaluated for prevention and treatment of seasonal and pandemic influenza A and B infections.

METHODS

Viral Growth Inhibition Assay

Infected A549 cells were used to evaluate the activities of CB-012 and oseltamivir against A/WSN/33 (H1N1), A/California/04/09 (H1N1), A/Wyoming/3/03 (H3N2), B/Lee/40/Victoria, and A/Vietnam/04 HALo (H5N1).

Pharmacokinetics

Plasma samples were collected following IV administration of CB-012 50 mg/kg in CD-1 mice. Concentrations of CB-012 in plasma were assessed using ELISA (TM capture, Fc detection).

METHODS (cont'd)

Prophylactic Efficacy

Lethal mouse influenza models (A/Texas/36/91 [H1N1] and A/Hong Kong/1/68 [H3N2]) were used to evaluate prophylactic efficacy in vivo. In the H1N1 model (n=5/cohort), a single IV dose of CB-012 (0.4–50 mg/kg) was evaluated when administered 4 hours prior to infection and when administered 28 days prior to infection. In the H3N2 model (n=5/cohort), a single IV dose of CB-012 (0.4–2 mg/kg) was administered 4 hours prior to infection. Efficacy was compared with that of oseltamivir 20 mg/kg orally twice daily (BID) for 5 days starting 8 hours post-infection and with controls. Survival and body weights were monitored for 14 days.

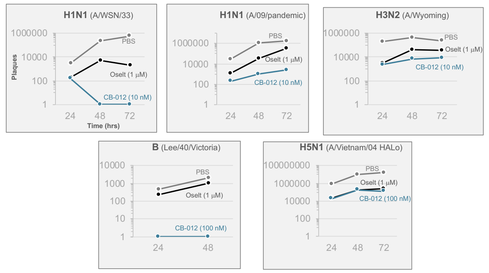
Treatment Efficacy

CB-012 treatment efficacy was evaluated in vivo using a lethal mouse influenza model infected with A/Texas/36/91 (H1N1) (n=5/cohort). A single IV dose of CB-012 (10 mg/kg) and oral oseltamivir 20 mg/kg BID for 5 days were administered starting 8–96 h post-infection. Survival was monitored for 14 days.

RESULTS

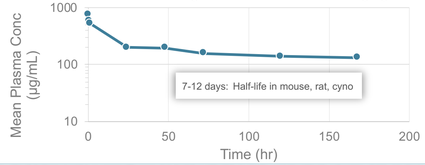
CB-012 at 10 nM or 100 nM reduced the amount of released infectious virus in supernatant 2- to 3,000-fold more efficiently than oseltamivir at 1000 nM. (**Fig. 2**).

Figure 2. CB-012 and oseltamivir activity in vitro against H1N1, H3N2, and H5N1.



CB-012 demonstrated a long terminal half-life ($t_{1/2}$, 10 d) and high sustained concentrations in plasma (**Fig. 3**)

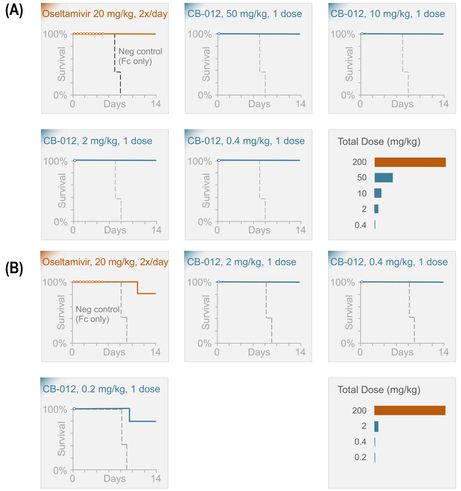
Figure 3. Plasma Concentrations After a Single IV Dose of CB-012 50 mg/kg in mice



RESULTS (cont'd)

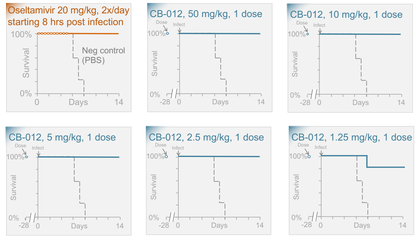
In short-term prophylaxis (4 hours prior to infection; A/Texas/36/91 [H1N1], A/Hong Kong/1/68 [H3N2]), a single 0.4-mg/kg dose of CB-012 demonstrated 100% protection against influenza (**Fig. 4**) while maintaining similar body weight compared to uninfected controls (data not shown).

Figure 4. In vivo Prophylactic Efficacy of Single Dose CB-012 Against Influenza (A) A/Texas/36/91 (H1N1) and (B) A/Hong Kong/1/68 (H3N2) Compared with Oseltamivir BID x 5 days.



CB-012 demonstrated a long duration of action in mice, where one 2.5 mg/kg dose 28 days prior to infection (A/Texas/36/91 [H1N1]) demonstrated 100% protection from death (**Fig 5**).

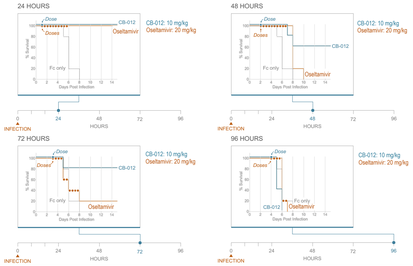
Figure 5. In vivo Prophylactic Efficacy of Single Dose CB-012 Administered 28 Days Prior to Influenza Challenge (A/Texas/36/91 [H1N1]) Compared with Oseltamivir BID x 5 days.



RESULTS (cont'd)

In treatment, single doses of CB-012 demonstrated superior protective efficacy versus oseltamivir BID for 5 days initiated 48 and 72 h post infection (**Fig 6**).

Figure 6. in vivo Treatment Efficacy of Single Dose CB-012 Against Influenza (A/Texas/36/91 [H1N1]) Compared with Oseltamivir BID x 5 days.



CONCLUSIONS

- CB-012 demonstrated potent activity against seasonal and pandemic influenza A strains and influenza B.
- CB-012 inhibited viral growth more efficiently than oseltamivir in vitro.
- Potent CB-012 in vitro activity translated to efficacy in lethal prophylactic and treatment influenza mouse models with a single dose.
- CB-012 displayed extended systemic exposure in mice that translated to long duration of action and efficacy in prophylaxis models.
- These findings with CB-012 validate the multimodal approach of Cloudbreak AVCs for the prevention and treatment of influenza.

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ACKNOWLEDGEMENTS

Editorial support was provided by T. Chung (Scribant Medical) and funded by Cidara Therapeutics, Inc.